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CASE REPORT

Typhoid rhabdomyolysis with acute renal failure and acute pancreatitis: a case report and review of the literature

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Summary We report a case of typhoid rhabdomyolysis with acute renal failure and acute pancreatitis in a 23-year-old Vietnamese male who was admitted to the intensive care unit with a 15-day history of fever followed by severe abdominal pain. On examination, the patient was febrile and his abdomen was diffusely tender. Serum creatinine was 533 μmol/L, pancreatic amylase 1800 U/L and lipase 900 U/L; the myoglobin blood level was high, which is associated with significant myoglobinuria. Blood, urine and stool culture yielded *Salmonella enterica* serovar typhi, which was sensitive to ceftriaxon, ampicillin and ciprofloxacin. Ceftriaxon was initiated for a total of 14 days. Subsequently, the patient maintained a good urine output with improved renal parameters and accordingly was discharged. In this report, we review the literature and discuss the pathogenesis of the disease thoroughly.

Introduction

Typhoid fever, also known as enteric fever, is a systemic infection caused by *Salmonella enterica* serovar typhi (*S. typhi*) or by the related but less virulent *Salmonella enterica* serovar paratyphi A. Complications occur in 10—15% of typhoid patients; gastrointestinal bleeding and intestinal perforation are most commonly involved.[1] Rare complications include rhabdomyolysis, acute renal failure,[2,3] pancreatitis,[4] meningitis,[1] myocarditis, pneumonia, arthritis, osteomyelitis and parotitis.[1,5] Although several organs can be affected in typhoid fever, the involvement of multiple organs in the same patient has rarely been reported in the literature. In this report, we present a case of typhoid fever complicated by rhabdomyolysis, acute renal failure and pancreatitis in a previously healthy young male. The aim of presenting this case is to highlight the spectrum of multiple organ involvement in typhoid fever, which, on rare occasions, could occur simultaneously in the same patient.

Case report

In June 2007, a 23-year-old Vietnamese male was admitted to the intensive care unit, after attending the emergency department, with a 15-day history of fever followed by severe abdominal pain and loss of appetite, accompanied

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Table 1 Laboratory findings during hospitalization

Day of admission	1	2	4	7	11	14	16
BUN (mmol/L)	24	31.1	33.2	29.8	17.4	9.4	6.9
Serum creatinine (μmol/l)	533	608	661	500	303	169	107
Serum Na^+ (mmol/L)	134	135	134	141	148	154	144
Serum K^+ (mmol/L)	3.6	3.7	3.4	3.2	3.5	3.9	4.5
Serum HCO_3 (mmol/L)	18	19	25	25	23	21	29
Serum Ca^{2+} (mmol/L)	2.1	2.2	2.17	2.25	2.19	2.35	2.32
Serum albumin (g/L)	36			34			32
Total protein (g/L)	67			71			69
ALT (IU/L)	124	115	140	139		69	
AST (IU/L)	300	241	262	116		45	
CPK (IU/L)	5350	3685	581	299	197	191	158
WBC $\times 10^9$//L	2.2	5.6	8.7	11.2	11.2	8.8	
PLT $\times 10^9$//L	45	38	58	95	194	282	
APTT (s)	49.4	46.7	37.5	37		33.7	
Pancreatic amylase (U/L)	1800	1200	563		163		80
Lipase (U/L)	900	630	324		123		64

PLT: platelets; APTT: activated partial thromboplastin time; BUN: blood urea nitrogen.

by nausea and vomiting. The patient was a healthy and active man who did not consume alcohol and had no known chronic illness. He had no history of drug abuse or blood transfusions, and no history of recent illnesses or contact with sick people. The patient arrived from Vietnam three weeks earlier. Upon physical examination, the patient appeared ill, was conscious and oriented, febrile and dehydrated. His pulse rate was 114 beat/min, his blood pressure was 110/70 mmHg and his temperature was 39.6 °C. His abdomen was diffusely tender without organomegaly; the rest of the physical examination was unremarkable. Initial investigations showed the white blood cell (WBC) count to be 2.2 $\times 10^9$/L, hemoglobin 12.3 g/dl and platelets 45 000/μl. Serum creatinine was 533 μmol/L, blood urea 24 mmol/L, serum sodium 134 mmol/L and potassium 3.6 mmol/L; pancreatic amylase was 1800 U/L (normal 15—55 U/L) and lipase was 900 U/L (normal 13—60 U/L). Liver function test showed normal total protein and albumen with abnormal liver enzymes (aspartate aminotransferases [ASTs] 300 IU/L; alanine aminotransferases [ALTs] 124 IU/L). Lactate dehydrogenase (LDH) was 2868 U/L (normal 240—480 U/L) and serum creatine phosphokinase (CPK) was 5350 IU/L (normal ≤190 IU/L). The myoglobin blood level was high, which is associated with significant myoglobinuria. A coagulation profile was normal. Tests for antinuclear antibodies, circulating immune complexes, ANCA and cryoglobulinemia were negative. Serum complements C3 and C4 were normal. Antibodies to hepatitis A, B and C viruses, and HIV were absent, whereas the Widal test was positive. Blood was sent to the laboratory for culture and sensitivity testing.

An abdominal ultrasonography showed normal-sized kidneys but could not visualize the pancreas, and a computerized tomography (CT) scan of the abdomen without contrast showed a bulky pancreas, whereas examination of the liver and biliary system showed no abnormalities.

The patient was admitted to the intensive care unit, as a case of acute pancreatitis and acute renal failure (ARF) secondary to rhabdomyolysis. Early and aggressive hydration was initiated together with furosemide infusion. Urinary output was measured hourly; the dose of furosemide infusion was adjusted according to this and the clinical status of the patient. As empirical therapy, intravenous (IV) tazocin (piperacillin-tazobactam) 2.25 g Q8 hrs was administered. Two days later, blood, urine and stool culture yielded *Salmonella enterica* serovar typhi, which was sensitive to ceftriaxon, ampicillin and ciprofloxacin. Ceftriaxon was initiated for a total of 14 days. The patient maintained a good urine output throughout the illness, averaging 2.5 l/day, and his renal parameters improved without dialysis, as shown in Table 1. Sixteen days after admission, he was discharged with normal renal function and normal CPK level.

Discussion

The spectrum of rhabdomyolysis causes is quite broad and includes disorders of a traumatic, metabolic, infectious, toxic and enzymatic origin. Salmonella infection is an infrequently reported cause of rhabdomyolysis;[6—8] typhoid rhabdomyolysis is especially rare. A MEDLINE search showed that only nine cases of typhoid rhabdomyolysis have been reported in the literature.[2,3,9—15] In the majority of cases, rhabdomyolysis is followed by acute renal failure, and represents a cause of significant morbidity and mortality. In 1977, Rheingold et al. reported the first case of rhabdomyolysis and acute renal failure as a complication of typhoid fever.[2]

Table 2 details characteristics of some reported cases of rhabdomyolysis associated with culture-proven typhoid fever. Manifestations of rhabdomyolysis can vary from subclinical to severe, depending upon the extent and severity of muscle damage. Symptoms can range from mild myalgia to severe pain with weakness. Our patient presented with fever and severe abdominal pain, which might mask rhabdomyolysis symptoms. Serum levels of CPK are a hallmark of rhabdomyolysis; confirmation of the diagnosis is accomplished by the detection of myoglobin in urine. All these elements were present in our patient.

The mechanism(s) responsible for rhabdomyolysis with Salmonella infection are poorly understood. Proposed mechanisms of Salmonella-induced rhabdomyolysis include

Table 2 Characteristics of patients with definite rhabdomyolysis associated with *Salmonella enterica* serovar typhi bacteremia

Reference	Year	Peak serum CPK level (IU/L)	Urine findings	Therapy	Complications; outcome
Rheingold et al. [2]	1977	17 260	Orthotolidine (+)	Ampicillin	Renal failure and hepatitis; partial recovery.
Barnes et al. [3]	1986	20 360	RBCs (4+), protein (+).	Ampicillin	Renal failure and hepatitis; recovered.
Rafik et al. [12]	2000	102 500	RBCs (3+), protein (+).	Ciprofloxacin	Renal failure, hepatitis, gastrointestinal bleeding and delirium; recovered.
Fisk et al. [14]	2004	42 165	Myoglobin (+)	Ceftriaxon	Renal failure; recovered.
Simcock D [15]	2004	18 477	Myoglobin (+)	Cefotaxime	Renal failure; recovered.
Khan et al. (present case)	2007	5350	Myoglobin (+)	Ceftriaxon	Renal failure, pancreatitis; recovered.

RBC: red blood cell.

tissue hypoxia caused by sepsis, toxin release, direct bacterial invasion of muscle, low oxidative and glycolytic enzyme activity, and activation of lysosomal enzymes.[16–18] Irrespective of the mechanism involved, a final common pathway of an increase in the intracellular concentration of calcium ions has been established.[19] Although some authors reported significant co-morbidities associated with the development of rhabdomyolysis, including chronic pulmonary disease, end-stage renal disease, chronic alcohol abuse and hypertension, our patient had no significant co-morbidities.[6,7,20]

Renal involvement is a rare manifestation of typhoid fever, occurring only in 2–3% of patients.[21] The spectrum of renal complications in typhoid fever includes cystitis, pyelitis, pyelonephritis, mild proteinuria and, less commonly, mild to severe glomerulonephritis, acute tubular necrosis and interstitial nephritis.[22–27] Recovery of *S. typhi* from urine is a rare event, even in areas endemic for this infection; it can be isolated from urine following a recent episode of typhoid fever, in chronic carrier states involving the urinary system and, occasionally, following localized urinary tract infection (UTI) due to *S. typhi*.[28] In this patient, *S. typhi* was isolated from his blood, stool and urine, which suggests that typhoid bacteremia was the cause.

Typhoid glomerulonephritis is a rare complication affecting 2–4% of typhoid patients in endemic areas and subjects traveling from endemic areas.[23] The actual incidence of this complication is probably underestimated, because renal tissue is seldom examined histologically and morphological evidence of glomerulonephritis can exist in the absence of clinical manifestations.[26] The pathogenesis of glomerulonephritis in typhoid fever is uncertain. Three important mechanisms are suggested: first, toxin-induced nephropathy;[22] second, immune complex glomerulonephritis;[23] third, direct invasion of *Salmonella enterica* serovar typhi. Renal biopsy studies in these patients have shown diffuse proliferative glomerulonephritis and immunoglobulin, C3 and Vi antigen deposits in the glomerular basement membrane.[29]

Acute renal failure in patients with typhoid fever has been described in several case reports; dehydration, shock and rhabdomyolysis are the most likely causes.[22] Other rare causes of renal failure include glomerulonephritis, acute tubular necrosis and interstitial nephritis.[22–27] An intrinsic toxic effect of Salmonella on the kidney is suggested by Van Doorn et al.[22] It was hypothesized that Salmonella toxic effects, in concert with activation of the renin-angiotensin axis and release of proinflammatory cytokines, produce renal perfusion disorders that impair renal function in a high number of patients with acute Salmonella gastroenteritis, even though the causes of renal failure in many patients are still uncertain and a multifactorial etiology cannot be ruled out. In the majority of cases, hemodialysis was required before renal failure resolved; in our patient, the most likely cause of renal failure was rhabdomyolysis and his renal failure was resolved without hemodialysis.

Asymptomatic hepatitis commonly occurs in typhoid fever, with most patients having only slightly elevated AST and ALT levels, and more than one-third having jaundice.[30] Our patient showed a high transaminase level, which returned to normal after completion of treatment.

Pancreatitis has been infrequently described in typhoid fever. Its spectrum ranges from biological abnormalities to pancreatic abscesses requiring surgery. Although the exact mechanism linking typhoid fever and acute pancreatitis is unknown, numerous potential explanations have been suggested. Some authors postulated that typhoid pancreatitis could represent the effect of the direct pancreatic localization of bacteria. Theoretically, this could happen through a hematogenous route, lymphatic route and transmural migration, via the biliary duct system, and from the duodenum via the main pancreatic duct. This is true, especially in patients with conditions predisposed to biliary stasis, such as cholelithiasis, choledocholithiasis and biliary duct abnormalities,[31–33] but our patient had no such predisposing conditions. Other possible mechanisms linking typhoid fever and acute pancreatitis include toxin-induced and immune-mediated pancreatitis.[34,35]

The treatment and prognosis of myoglobinuric renal failure and acute pancreatitis associated with typhoid fever remain unclear. According to our review of reported cases, in addition to the current case, it seems to have a benign course. The most important aspect of treatment is to recognize the condition promptly, initiate early proper antibiotics and provide good supportive care. Monitoring any complications and instituting appropriate therapy are also critical.

In summary, typhoid fever has potentially serious complications that might involve multiple organs simultaneously in the same patient. Early recognition, and supportive and adequate antimicrobial treatment are mandatory for these patients.

Conflict of interest: No conflict of interest to declare.

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